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A Complex Case of Relapsed Pre-XDR Tuberculosis Complicated by Pregnancy and Congenital Anomaly: Management and Lessons Learned

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ABSTRACT

Background: The emergence of drug-resistant tuberculosis, particularly the cases of multidrug-resistant (MDR-TB) and pre-extensively drug-resistant (pre-XDR-TB), proves to be a tremendous barrier to the world's control of TB programs. In addition, if these cases are manifested with the problems of pregnancy and comorbidities, they will be extremely hard to deal with.

Case Presentation: We report the case of a 28-year-old female with a chronic pulmonary tuberculosis infection. Initially, she experienced a partial response to a first-line Category-I regimen, which was later followed by a Category-II retreatment regimen that also did not work for her. She was diagnosed with Rifampicin-resistant TB (RR-TB) via GeneXpert and was then cured with a standard MDR-TB regimen. Nevertheless, relapses occurred six months after the treatment was deemed successful. An individualized MDR-TB regimen was started when she was found to be pregnant. Her pregnancy was complicated by poorly controlled diabetes mellitus that required treatment with insulin. A multidisciplinary team, including Pulmonology and Fetomaternal Medicine, managed her case. She delivered a girl baby with a cleft palate that was linked to uncontrolled diabetes. The patient continued her MDR-TB treatment without any signs of perinatal TB transmission.

Conclusion: The instance appears to demonstrate adequately the fundamental requirement for rapid drug susceptibility testing (DST), the extremely high relapse risk in drug-resistant TB, and the highly significant need for a multidisciplinary approach to manage MDR-TB in pregnant women. Additionally, it brings home the teratogenic risks tied to uncontrolled maternal diabetes and the necessity for very close monitoring and counseling in such complicated circumstances.

Keywords: Multidrug-Resistant Tuberculosis (MDR-TB); Pre-Extensively Drug-Resistant TB (Pre-XDR-TB); Pregnancy; Congenital Anomaly

Introduction

Tuberculosis, also known as TB, is still a major health problem worldwide, and according to the estimates for the year 2022, there were 10.6 million new TB cases and 1.3 million deaths.[1] The distribution of the disease is not the same in all countries; poor and middle-income nations suffer the most, Pakistan being the most clear example of such a crisis, as it is the 5th highest TB burden country in the world and facing an epidemic of MDR-TB (multidrug-resistant TB) and HIV co-infection at the same time.[1] The World Health Organization (WHO) estimates that in Pakistan, the percentages of the new cases of TB diagnosed as MDR or rifampicin-resistant (RR-TB) are 3.4% and 17% respectively, of the previously treated cases, which points to a very serious and continuous transmission of drug-resistant strains of TB in the community.[1,2]

MDR-TB, which is an acronym of "multi drug resistant tuberculosis," outlines the most severe stage of the disease by signifying the resistance to isoniazid and rifampicin, the two strongest first-line anti-TB drugs.[3] Its treatment, thereby, requires the application of second-line drugs, which are known for the longer treatment periods that generally range from 9 to 18 months, increased costs, greater drug-related toxicities, and lower efficacies when compared to first-line regimens. The timeline for treatment is further lengthened and made more costly with the advent of advanced drug resistance. Pre-extensively drug-resistant TB (pre-XDR-TB), for instance, consists of cases that are resistant to rifampicin and isoniazid but not to any fluoroquinolone (levofloxacin or moxifloxacin), which are termed the backbone of modern MDR-TB therapies.[4,5] Such a resistance pattern greatly confines the treatment options available, makes the design of such regimens more difficult, and is invariably linked to worse treatment outcomes, higher death rates, and greater risks of the disease being transmitted.[6] In fact, the progression from MDR-TB to pre-XDR-TB is very often due to programmatic shortcomings like poor patient compliance, use of improper drug combinations, and late diagnosis owing to the unavailability of rapid molecular drug susceptibility testing.

The clinical handling of MDR-TB and pre-XDR-TB always presents complexities, but in certain situations, especially with pregnant women, this difficulty is multiplied to an extreme level. Tuberculosis coupled with pregnancy is a condition that poses the most difficult therapeutic, ethical, and logistical issues.[7] From a physiological perspective, pregnancy alters drug pharmacokinetics, such as increased volume of distribution, faster renal clearance, and altered protein binding, which might result in lower serum concentrations of anti-tuberculosis drugs, thereby endangering the patient with underexposure and resistance development.[8] Regarding safety, the development of the fetus might be endangered if some second-line anti-TB drugs are given, particularly if they are aminoglycosides (for example, kanamycin and amikacin), which are notorious for causing hearing loss, and drugs with possible teratogenicity, even though the extent of the effect is not universally known for all, still, a thorough risk-benefit assessment is mandated.[9]

Doctors face a very difficult moral dilemma in this case. If the developing baby has a pregnant mother with drug-resistant TB and the baby is untreated or the drug is given late, then the mother will have a progressive disease, which might lead to her death, and the baby will have the risks of being born too soon, weighing less than normal, and having congenital TB.[10,11] However, the mother receiving a heavy cocktail of second-line drugs for drug-resistant TB means the baby could be misshapen or even poisoned. Such situations in the past have made doctors face dilemmas where one solution has been the termination of pregnancy for the sake of treatment. But advances in WHO guidelines and growing medical personnel experience have now allowed the treatment of MDR/RR-TB in pregnant women with regimens carefully selected and under very close medical supervision; therefore, the great need for the aforementioned specialists of the multidisciplinary team consisting of pulmonologists, obstetricians, infectious disease specialists, and TB experts has been highlighted. The objective is to provide the mother with the most potent treatment possible while causing the least harm to the fetus, which is often the case with oral agents such as later-generation fluoroquinolones, linezolid, and cycloserine, while avoiding injectable aminoglycosides.[12]

This clinical narrative, which was pretty tough to write, presents a very illustrative case from Pakistan that highlights the challenges of TB control in a high-burden setting. The case report describes the extremely long journey of the 28-year-old woman who had to undergo first-line and second-line treatments, which all failed, one after the other, and finally, she was diagnosed with relapsed pre-XDR-TB. Besides her lengthy clinical course, an unplanned pregnancy happened during her treatment for relapsed disease, which was later made more challenging by the development of uncontrolled gestational diabetes. This case, along with its narrative, provides a comprehensive view of the real-world obstacles in diagnosing and treating complex drug-resistant TB, the practicalities and complications of treatment during pregnancy, and the crucial role of a connected, multi-specialist team in promoting maternal and fetal health. Our discussion is intended to highlight the major lessons for clinical practice and reinforce the urgent need for robust TB control programs equipped with rapid diagnostics, effective drugs, and patient-centered care models.

Case Presentation

A 28-year-old woman, who used to be in good health, went to a private doctor with the symptoms of fever and

cough producing phlegm lasting for two weeks. After a continuous period of 15 days on unsupervised antibiotics without showing any signs of improvement, she was sent to a governmental clinic. There, the patient was identified as having lung tuberculosis and started on the Class-I first-line anti-TB treatment (2HRZE/4HR) as a new incidence.

She underwent the six-month treatment but had symptoms reappearing after three months of finishing the treatment. She had clinical deterioration and so went to a tertiary care hospital where she was put on the Category-II retreatment regimen (2HRZES/1HRZE/5HRE) that contains streptomycin. She finished this eight-month treatment.

After some months, the patient once again presented with cough, weight loss, body aches, and fever. A PMDT unit (Programmatic Management of Drug-Resistant Tuberculosis) was the place to which she was sent. Chest X-ray showed left lower lobe consolidation. The microscopic examination of the sputum smear was positive for Acid-Fast Bacilli (AFB 2+). The GeneXpert MTB/RIF assay not only confirmed the presence of Mycobacterium tuberculosis complex but also detected Rifampicin resistance (RR-TB). In addition, a specimen was dispatched for liquid culture and phenotypic Drug Susceptibility Testing (DST).

Pending DST results, she was immediately started on a standardized MDR-TB regimen consisting of Intramuscular Kanamycin (Km), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserine (Cs), Ethambutol (E), and Pyridoxine.

She showed a remarkable clinical and microbiological response. She gained weight, her cough resolved, and her sputum converted to AFB-negative after the second month of therapy. Chest radiograph showed significant improvement. She completed the 20-month regimen and was declared "treatment completed."

The patient developed a cough, fever, hemoptysis, progressive dyspnea, and loss of weight six months after the treatment was completed. She called the PMDT unit directly. Sputum AFB was positive, and GeneXpert again confirmed the presence of the MTB complex with Rifampicin resistance. Because of the history of the previous treatment of MDR-TB and the early relapse, she was classified as having Relapsed RR/MDR-TB. The patient was put on an individualized MDR-TB regimen taking into account her previous treatment history and the local drug resistance patterns. The regimen comprised Bedaquiline (Bdq), Linezolid (Lzd), Levofloxacin (Lfx), Cycloserine (Cs), and Clofazimine (Cfz).

In the third month of this regimen (at the intensive phase), she had a positive result in her routine urine pregnancy test. The Fetomaternal medicine team was immediately consulted. After a thorough discussion, the patient decided to continue the pregnancy. The anti-TB regimen was looked at again; all medications were found to be either compatible with pregnancy or to have a favorable risk-benefit profile when compared to untreated MDR-TB. Moreover, her pregnancy was further complicated by the development of uncontrolled diabetes mellitus, which necessitated treatment with subcutaneous insulin. A multidisciplinary team of pulmonologists, obstetricians, and endocrinologists was involved in her care and closely monitored her throughout her pregnancy.

At the 38-week mark of her pregnancy, she gave birth to a female baby through natural vaginal delivery. There were no signs, either clinical or microbiological, of the transfer of tuberculosis from the mother to the child during the perinatal period. However, the newborn was found to have a unilateral cleft palate. This birth defect was linked to the maternal diabetes being uncontrolled during the first trimester, which is a well-known risk factor.

The patient carried on and completed her personalized MDR-TB treatment plan under supervision. She experienced no major drug side effects throughout the rest of her treatment that would necessitate changing the regimen.

Discussion

This patient's clinical journey vividly represents the enormous difficulties that drug-resistant tuberculosis management faces in places like Pakistan, which have a high prevalence of the disease. Her case sheds light on several important points for doctors and health programs. Most importantly, it highlights the dangers of empirical management and the absolute requirement for universal drug susceptibility testing (DST).[13] The patient's initial treatment with first-line regimens, without confirmation of drug susceptibility, most likely led to the sequential amplification of resistance, which is one of the well-known consequences of inadequate initial therapy. This progression from a new case to MDR-TB and then to pre-XDR-TB could have been prevented if the rapid molecular test, such as the GeneXpert MTB/RIF assay, had been implemented early. Our case very strongly supports the current WHO recommendation and the necessity for a national policy in Pakistan to promote such testing at the point of initial diagnosis for all TB patients, not just those with risk factors for drug resistance.[14,15]

Secondly, this case exemplifies the high risk of relapse and treatment failure in drug-resistant TB, particularly when management is not guided by comprehensive DST. The patient's initial favorable response to the standardized MDR-TB regimen, followed by a rapid relapse within six months, is highly suggestive of undetected pre-existing fluoroquinolone resistance.[16] The initial standardized regimen she received (containing Kanamycin and Levofloxacin) would have been compromised if she had pre-XDR-TB from the outset. This outcome underscores a significant limitation of standardized regimens in an era of advancing resistance and powerfully argues for the paramount importance of baseline DST, including to

second-line drugs, to guide a truly individualized therapy from the very beginning of treatment for RR/MDR-TB.[3] The subsequent success of her second MDR-TB regimen, tailored to her history and likely including more effective agents such as Bedaquiline and Linezolid, highlights the superior efficacy of individualized treatment informed by a full resistance profile.[17]

Perhaps the most complex dimension of this case is the management of MDR-TB in pregnancy. Our patient's experience demonstrates that with a carefully selected regimen and a dedicated multidisciplinary team, successful treatment outcomes are achievable for both the mother and the child. The management required careful consideration of the teratogenic and toxic potentials of second-line drugs. As per recent WHO guidelines, drugs like levofloxacin and linezolid, while requiring careful risk-benefit analysis, can be used when indicated, as the risk of untreated MDR-TB far outweighs the potential risk of these medications.[11] The collaborative approach between the Pulmonology and Fetomaternal medicine teams was instrumental in navigating these complex decisions, ensuring optimal care for the mother while vigilantly monitoring fetal well-being.[10] The absence of perinatal TB transmission is a testament to the success of this approach.

Finally, the case highlights the critical role of comorbidities. The emergence of uncontrolled gestational diabetes introduced a significant comorbidity that directly impacted the obstetric outcome. Poorly controlled diabetes in the first trimester is a well-established risk factor for congenital anomalies, including cleft palate, which was observed in the neonate.[9] This unfortunate outcome underscores that managing TB in isolation is often insufficient. It highlights the imperative for rigorous screening and aggressive management of comorbidities, especially in pregnant patients, to mitigate adverse outcomes beyond those directly related to tuberculosis.[18]

Conclusion

To conclude, the management of a pregnant patient with diabetes who relapsed from pre-extensively drug-resistant tuberculosis is one of the most challenging cases in modern pulmonology and infectious disease. This case clearly underscores the conditions critical to success in such complex situations. First of all, it points to early and thorough drug susceptibility testing as the basis for therapy from the very start and as a measure against the escalation of resistance. Second, it points to the need for setting up suitable, individualized, and non-standardized regimens for drug-resistant TB very soon. The patient's journey was effectively the success of a committed, multidisciplinary team approach, which included recognizing the contributions of pulmonology, fetomaternal medicine, and endocrinology to maternal treatment and fetal welfare. In addition, the case shows that the aggressive treatment of comorbidities like diabetes is not merely ancillary but an integral part of the process of preventing adverse obstetric outcomes and ensuring the health of both mother and child. Lastly, none of these interventions can be effective without the continuous counseling of the patient and the provision of strong psychosocial support systems that empower and guide individuals through the prolonged and difficult circumstances of treatment for drug-resistant TB. Admitting to these core principles is key to raising the standards in these most intricate cases happening in high-burden places like Pakistan.

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